Reducing the Risk of Alzheimer’s Disease: Knowns and Unknowns

Margaret Gatz, Ph.D., and Joanne Steuer, Ph.D.

University of Southern California

Contact Information

Margaret Gatz, Ph.D.
Affiliation: Department of Psychology, University of Southern California
Mailing Address: Department of Psychology, University of Southern California, 3620 S. McClintock Avenue, Los Angeles CA 90089-1061
Email: gatz@usc.edu

Joanne Steuer, Ph.D.
Affiliation: University of Southern California
Mailing Address: PO Box 931808, Los Angeles, CA 90093-1808
Email: jsteuer@usc.edu

Acknowledgements

This paper is a revision of a plenary address at the American Psychological Association convention in Washington, D.C. in August 2011. The work was partially supported by the National Institutes of Health [grant number R01 AG08724] and the Alzheimer’s Association [Zenith Award ZEN-02-3895].
Abstract

**Purpose of the Study:** Alzheimer’s disease affects approximately 10% of people over age 65. We currently do not know how to prevent this disease. However, we are beginning to believe there are ways to delay its onset and thus reduce the number of people who develop Alzheimer’s. **Design and Methods:** This paper is a summary of what we know about modifiable risk factors that might delay the onset of Alzheimer’s disease, other dementias, and cognitive decline more generally. **Results:** Genetic factors play a significant role, accounting for more than half of the risk of developing Alzheimer’s disease. However, environment, lifestyle and chance also contribute substantially to risk. Risk factors in early life include disadvantages such as parental socioeconomic status, poor nutrition, inflammation and disease. In midlife, diabetes, elevated cholesterol and being overweight add risk. On the other hand, across the lifespan, education, complexity of work, physical activity, and possibly diet may be protective. Protective effects for Alzheimer’s disease related to leisure activities and cognitive stimulation remain controversial. **Implications:** Cautious optimism is warranted around improving cognitive health in older adulthood through modifying early and mid-life risk and protective factors. At the same time, we need to avoid making claims that go beyond the evidence.
The purpose of this paper is to provide a summary of the current state of knowledge about modifiable risk factors for Alzheimer’s disease and for cognitive decline more generally. Since there are no known cures for Alzheimer’s disease or dementia at this time, modifying risk is our best option to reduce the number of people affected by these diseases.

Alzheimer’s affects approximately 10% of people over the age of 65, with rate of the disease increasing exponentially with age. Last year, 2011, the first Baby Boomers, one of the largest cohorts of all time, entered that age group. By 2020 the entire first cohort of Baby Boomers will have reached or passed age 65. By 2013, the proportion of the U.S. population over age 65 will be larger than the proportion under age 15. Estimates from the US Census Bureau are that the population age 65 and over will double to about 72 million by 2033. By 2030 and beyond, the proportion of adults age 85 and over, who are at the highest risk of Alzheimer’s, will increase. And, if 10% of older adults have a particular disease, without assuming any change in the rate of the disorder, the number of older adults with that condition is going to explode.

Of course, if advances were made in prevention or treatment this picture could improve. On the other hand if modifiable risk factors, such as diabetes and obesity, continue to rise among the middle-aged the picture could look even worse. Moreover, as the number of persons living with dementia increases, so does the number of family caregivers affected and the burden on the health care system.

The term “dementia” is used to describe a group of diseases with onset in old age and characterized by progressive loss of cognitive function. Causes of dementia include Alzheimer’s disease, stroke (the primary cause of vascular dementia), Lewy body disease, and others less common. The focus here is primarily on Alzheimer’s disease which accounts for about two thirds of dementia cases in older adults.

We do not fully know what causes Alzheimer’s disease, although we have a pretty well developed picture of the cascade of events in the brain that characterize the disease. The cascade includes deposition of amyloid plaques and neurofibrillary tangles, the two hallmarks of Alzheimer’s disease. This leads to oxidative injury, inflammation and neurotransmitter deficits, specifically acetylcholine, all of which disrupt communication
between neurons and eventually leads to cell loss, which is apparent as brain atrophy. This series of events suggests certain targets for treatment or prevention, such as reducing beta amyloid production, enhancing cholinergic function, or use of anti-inflammatory agents or anti-oxidants, which have helped to focus research. We also know that these changes begin well before the disease is detected clinically.

After age, the strongest risk factor for Alzheimer’s disease is genetic. For a tiny number of cases, there are known genetic mutations that account for the disease. These cases typically have early age of onset, that is, before age 60. But for the vast majority of Alzheimer’s disease there are no specific genes that are the cause of the disease and the age of onset is later.

There are however, a number of different genes that are identified as risk factor or susceptibility genes, including the most well-established, apolipoprotein E (APOE), where the e4 allele of this genotype is associated with increased risk of developing Alzheimer’s disease. Results for other susceptibility genes continue to be mixed, and efforts are underway to conduct larger scale studies in order to achieve greater consistency. The susceptibility genes tend to be related to amyloid beta regulation, lipid transport, oxidative stress and immune function.

Based on these findings, it seems likely that many genes each contribute a small amount to risk for Alzheimer’s disease. Results from twin and family studies allow us to estimate the overall importance of genetic factors. Biometric twin analyses indicate that somewhere in the range of 70% of variation in liability for Alzheimer’s disease can be explained by genetic factors. A summary of what is known about the genetics of risk for Alzheimer’s disease can be found in Tanzi (2012).

To illustrate the importance of genetic influences, we calculated probandwise concordance rates for dementia using individuals aged 65 and older from the Study of Dementia in Swedish Twins (Gatz, Reynolds, et al., 2006; Gatz, 2007). To put concordance rates for twins into context, we estimated the chance that any two unrelated, randomly paired, individuals of the same age and gender would both be demented. This falls at about 16%. Having a fraternal twin with Alzheimer’s disease nearly doubles the risk of developing the disease to
about 30%. Reviews of family studies show a similar increase in risk associated with having a first degree relative with Alzheimer’s disease (Green et al., 2002). Finally, having an identical twin with Alzheimer’s disease doubles the risk again, and puts one’s risk of developing Alzheimer’s disease upwards of 59%.

However, not all twins become concordant, and even among concordant monozygotic pairs from the Study of Dementia in Swedish Twins there can be impressive differences in age of onset. Looking at age of onset in 14 monozygotic twin pairs concordant for Alzheimer’s disease, average difference in age of onset between identical pairs was 3-4 years, with a range from the same year to 16 years difference. This observation is extremely important with respect to indicating a role for life style, environment, and chance in developing Alzheimer’s disease.

One way of thinking about non-genetic risk and protective factors is with respect to their influence on the age-related trajectory of cognition. Figure 1 illustrates the gradual loss of cognitive reserve over age, with an individual crossing the threshold first into mild cognitive impairment and subsequently into dementia. Risk factors increase the rate of loss. Protective factors slow the rate of loss.

There have been several recent efforts to form a consensus about risk and protective factors for Alzheimer’s disease, cognitive decline and/or cognitive problems. The Healthy Brain Initiative was a joint activity of the Centers for Disease Control and Prevention and the Alzheimer’s Association (2007). The project began with an expert conference to review the state of knowledge. National Institute of Health (NIH) recently published a state of the science statement (Daviglus, et al., 2010). NIH consensus and state of the science statements are prepared by independent no-advocate panels that are provided with a systematic literature review and presentations by investigators in the field. In 2008, Psychological Science in the Public Interest (PSPI) published a monograph by Hertzog, Kramer, Wilson and Lindenberger focused on whether individuals’ behaviors and their environmental contexts that might be categorized as cognitively enriching are associated with reduced risk of dementia. In 2012, Cold Spring Harbor Perspectives in Medicine published a special issue on the biology of Alzheimer’s disease including a review of factors that increase and reduce the risk of Alzheimer disease (Mayeux
& Stern, 2012).

Figure 2 presents a scorecard showing how each of these sources evaluated the evidence base. If a cell is blank, it is because the factor was within the scope of the review but the panel explicitly or implicitly concluded there was insufficient evidence. There are a number of limitations to the literature. Many reports are observational. The best are prospective longitudinal studies where a defined cohort is followed for many years, with risk and protective factors measured prior to the onset of cognitive decline. But there is still the problem of confounding variables, measured and unmeasured. While clinical trials are in many respects the gold standard, they suffer from being short in duration. Particularly since the disease may begin years before its diagnosis, and some of the influences in which we are interested may have their effects far earlier in life, it is infeasible to design a clinical trial. Finally, it is important not to assume that, because a factor is related to better cognition in healthy elderly persons, it will reduce risk for dementia.

The final column on the scorecard presents results from the the Study of Dementia in Swedish Twins. This is a prospective observational study. When the twins enrolled in the twin registry in mid-life, in 1961 or in 1973, they completed questionnaires that include information relevant to risk and protective factors for dementia. Information about health conditions was also available from linkage of the twin registry to national health registries. The twins were assessed for dementia when they were old. Data were analyzed in two ways. First, as any case-control study, all of those who develop dementia (cases) are compared with all of those who do not (controls). Second, in a co-twin control design, focus is on twin pairs where one twin has developed Alzheimer’s disease and co-twin has not. In this design, differences within twin pairs must be due to non-shared environment. The most strict design is a co-twin control design with monozygotic twins only. When results are significant for case-control but not for co-twin control, it suggests that the case-control results in part reflect confounding by genetic or other familial influences.

**Vascular Risk Factors**

Vascular risk factors such as heart disease, elevated cholesterol and diabetes have been established as
important for Alzheimer’s disease, not only for vascular dementia. These risk factors were at the top of the CDC and Mayeux and Stern lists as risk factors for Alzheimer’s disease, and diabetes in particular was singled out by NIH.

**Diabetes.** In the Study of Dementia in Swedish Twins, diabetes was a significant risk factor for Alzheimer’s disease and for vascular dementia in traditional case-control analyses and for total dementia in a co-twin control design. Midlife diabetes has a stronger effect than late life diabetes (Xu et al. 2009).

Adjusting for age, sex, education, stroke, heart disease, hypertension and BMI, odds ratio for midlife diabetes in the case-control analysis of Alzheimer’s disease was 2.25 (95% CI 1.25-3.92) compared with an odds ratio for later life onset diabetes of 1.56 (95% CI 1.05-2.32). For vascular dementia the odd ratios were 3.94 (95% CI 1.90-8.15) for midlife onset of diabetes and 1.62 (95% CI 0.92-2.80) for late life onset. Similarly, in the co-twin control study, adjusting for sex and education, midlife onset of diabetes was a significant risk factor for total dementia, OR 2.51 (95% CI 1.10-5.72), while late life onset of diabetes does not significantly increase risk of dementia, OR 1.23 (95% CI 0.66-2.65).

In the Honolulu-Asia Aging Study, not only was mid-life diabetes found to be a risk factor for dementia, but also both hippocampal atrophy—a neurodegenerative change characteristic of Alzheimer’s disease—and neuroanatomic markers of vascular brain damage could be seen in the brains of older men with Type 2 diabetes (Korf et al., 2006). These findings suggest that the mechanism for increased risk associated with diabetes lies in the neurophysiological effects of diabetes on the brain.

**Cardiovascular disease.** In the Swedish twins, during the first three years after hospitalization for non-stroke cardiovascular disease, non-stroke cardiovascular disease was a significant risk factor for vascular dementia, OR 3.64 (95%CI 2.01-6.57) but not a significant risk factor for Alzheimer’s disease, OR 1.48 (95%CI .83-2.64) (Eriksson et al., 2010). However, for twins with the e4 allele of APOE, cardiovascular disease was a significant risk factor Alzheimer’s disease, OR 2.39 (95%CI 1.15-4.96) but not for those without the APOE e4
allele OR .76 (95%CI 0.24-2.42). Significant risk for total dementia was also found in the total sample in the co-twin design, OR 1.86 (95% CI 1.11-3.13).

**Body Mass Index.** In the Swedish twins, midlife overweight, OR 1.91 (95%CI 1.30-2.80) and obesity, OR 3.43 (95% CI 1.49-7.90) vs. normal body mass index (BMI), adjusted for age, sex, education, diabetes, hypertension, stroke and heart disease, were significant risk factors for Alzheimer’s disease (Xu et al., 2011). Overweight was defined as BMI 25-30 and obesity as BMI greater than 30. Midlife obesity, OR 3.50 (95%CI 1.36-8.99) but not overweight was a significant risk factor for vascular dementia. In the co-twin control design, using 137 pairs discordant for dementia and controlling for sex, education, diabetes, hypertension, stroke and heart disease, the results were attenuated, overweight, OR 1.10 (95% CI 0.68-3.30); obesity 1.62 (95% CI 0.65-6.94) suggesting that genetic and early life environmental factors may contribute to the association between high midlife BMI and dementia. In other analyses, non-demented twins with higher midlife BMI scores had significantly steeper longitudinal cognitive decline (Dahl et al., 2010).

**Cholesterol.** In a study of incident dementia in Swedish twins, pairs of twins participating in longitudinal cognitive testing were identified, in which both members of the pair were cognitively intact at baseline and subsequently one member of the pair developed dementia, while the other twin continued to test with normal cognition. In these pairs, higher total cholesterol, t=-2.4 (p .0253), and apoB levels, t=-3.02 (p. 0062) were observed at baseline in the twin who subsequently developed dementia (Gatz et al., 2010). ApoB is the primary protein component in low density lipoprotein or LDL cholesterol. Complementing these findings, the NIH review found some evidence that use of statins decreased risk of Alzheimer’s disease (Daviglus et al., 2010).

In summary, there is strong and consistent evidence for the role of vascular risk factors in increasing risk of Alzheimer’s disease and of total dementia, especially when the vascular risk factor is present in mid-life. Midlife obesity, inadequately treated diabetes, and high cholesterol are becoming more frequent in this country, especially in traditionally under-represented minorities, where health disparities are already a huge concern. The implication is a greater rise in rates of Alzheimer’s disease.
Depression

There has been considerable attention to depression as a risk factor for dementia, and depression is listed by NIH and PSPI on the scorecard as a risk factor. Data from the Study of Dementia in Swedish Twins also shows a history of depression to be a significant risk factor for dementia, with rate of depression approximately three times higher in Alzheimer’s disease cases compared to their non-demented co-twins (Brommelhoff et al., 2009). However, for the dementia cases, over half of the depression had its first age of onset within five years of onset of the dementia. In contrast, for the cognitively intact co-twins, three quarters of those who had a history of depression had their first age of onset more than 10 years prior to the proband’s age of onset. Therefore, it appears that to a large extent, depression is a prodrome, that is, an early symptom of the developing dementia, not a risk factor. On the other hand, in Swedish twin data, both stress and neuroticism, as indicators of chronic psychological distress are risk factors for cognitive impairment (Crowe et al., 2006, Crowe et al., 2007).

Inflammation

Finch (Finch & Crimmins, 2004; Finch & Morgan, 2007) has championed the point of view that inflammation during early life has an effect on Alzheimer’s disease risk and mortality. As the twin registry in 1963 asked twins about their tooth loss prior to age 35, Finch suggested that the relationship between periodontal disease, one source of chronic inflammation, and dementia be investigated. Examining the records of over 100 pairs of identical twins discordant for dementia showed that the twin who developed dementia was significantly more likely to have been the one to have lost more teeth, compared to their non-demented co-twin, OR 3.60 (95% CI 1.34-9.70) (Gatz, Mortimer, et al., 2006). In a case-control analysis, other indicators of early disadvantage including parental socioeconomic status, the individual’s own level of education, and adult height each contributed cumulatively to risk of Alzheimer’s disease but did not explain the effect of tooth loss. Others, including the Normative Aging Study in Boston (Kaye et al., 2010), have gone on to replicate the finding about tooth loss.

The role of inflammation may also be studied by directly examining inflammatory biomarkers. In the
twin data, there was not a significant association between inflammatory biomarkers CRP or IL6, with levels measured on average 4.3 years before dementia onset, and the risk of future Alzheimer’s disease or dementia (Eriksson et al., 2011). Data for biomarkers in early life are not available for the twins. It is presumed that exposure to high inflammatory load matters most in early years of life.

**Education**

Education is among the most studied and reliable protective factors. Using Swedish twin data, education was examined in case control and co-twin control samples for Alzheimer’s disease and for total dementia. In the co-twin control design, with 100 identical twin pairs, where one twin had dementia and the co-twin was cognitively intact, education was significantly higher for the twin that did not develop dementia, OR 0.36 (95% CI 0.20-0.64). Many pairs had the same amount of education, but when pairs did differ, it was nearly three times more often that the unaffected twin had the higher education (Gatz, Mortimer et al.; 2006). Results were similar for Alzheimer’s disease alone.

The ECLipSE (Epidemiological Clinicopathological Studies in Europe) Collaborative (Brayne et al., 2010) looked at education and post mortem dementia pathology. More years of education were related to lower risk of dementia but were unrelated to neuropathological variables associated with Alzheimer’s disease or with vascular pathology. In other words, education did not protect the person against neurodegeneration; rather, it lessened the clinical expression of that pathology such that education permits better compensation for brain pathology.

**Cognitive Engagement**

One of the most popular putatively protective factors for Alzheimer’s disease is cognitively engaging activities during leisure time, although expert consensus provides a more mixed picture of the effectiveness of cognitive interventions to improve cognitive function and especially to delay onset of cognitive impairment (Daviglus et al., 2010). The 1967 Swedish Twin Registry questionnaire included a list of leisure activities. Controlling for education, in a co-twin control design, greater overall engagement in leisure activities was
protective with respect to subsequent Alzheimer’s disease (Crowe et al., 2003). Further analyses showed that this finding was specific to women and was especially marked for the subscale comprised of Intellectual-Cultural activities—reading, radio or TV, social visits and cultural activities—with OR 0.63 (95% CI 0.39-1.00). In subsequent analyses with the sample of 100 discordant pairs of MZ twins, cognitively stimulating leisure activities were not significantly related to Alzheimer’s disease or to dementia (Gatz, Mortimer, et al.; 2006).

The popular press gives a great deal of attention to cognitive training as a means to reduce dementia risk, and there is a richness of computerized and on-line cognitive exercises implying these can preserve intact cognitive functioning. There are well-designed studies of cognitive training directed toward those who are not demented. For example, Lövdén et al. (2012) have shown an effect on hippocampal volume among non-demented men receiving cognitively demanding spatial navigation training. What we do not know is whether these interventions will delay the onset of Alzheimer’s disease (Daviglus et al., 2010; Unverzagt et al., 2012), either through enduring changes effected in the brain or through providing compensation for any brain pathology that might later emerge. Thus, it seems that despite some provocative positive results, the area of leisure activities and cognitive enrichment is particularly fraught with hype.

**Occupation**

Far less attention has been paid to cognitive engagement in the course of one’s occupation as compared to leisure. Yet one might argue that work rather than leisure is where people spend a lot of time during midlife. Andel and colleagues (2005) applied to the Swedish twins a system of coding occupations that links each Swedish occupation code to its corresponding U.S. Census Code and in turn to extent to which each occupation involves complexity of work with Data, People, and Things. The prediction was that twins whose occupations involved greater complexity of work with data should be at less risk for Alzheimer’s disease and other dementias. There was a tendency in that direction, significant for Alzheimer’s disease, OR 0.17 (95%CI 0.15, 0.57) but not for all dementias, and a much stronger effect for complexity of work with people, which was significantly protective for both Alzheimer’s disease, OR 0.05 (95%CI 0.01, 0.35), and for all dementia, OR 0.47
(95% CI 0.25, 0.88).

Notably, work with data is coded as complex when it entails synthesizing and analyzing. Work with people is coded as complex when it entails mentoring, negotiating, instructing, supervising, or persuading, which are not only interpersonal (as implied by the word “people”) but also complex problem solving skills.

Similarly to the ECLipSE Collaborative findings for education (Brayne et al., 2010), data from the USC Alzheimer’s Disease Research Center indicated that high complexity of work with data and people predicted faster rates of cognitive decline in patients with confirmed Alzheimer’s disease diagnosis (Andel et al., 2006). Thus the protective effect of complexity of work may lie in better compensation for brain pathology, essentially postponing the clinical diagnosis of dementia.

**Physical Exercise**

In the various expert reviews, physical exercise consistently shows a strong protective effect. The 1967 Swedish Twin Registry questionnaire asked about physical exercise; therefore, the relationship between physical exercise and dementia was analyzed in case control and co-twin control samples. Adjusting for age, sex, education, smoking, alcohol, fruits and vegetables in diet, BMI and angina pectoris, both light exercise, such as gardening or walking were associated with reduced odds for dementia, OR 0.63 (95% CI 0.43-0.91) as was regular exercise involving sports OR 0.34, (95%CI 0.16-0.72) when compared to hardly any exercise (Andel et al., 2008). On the other hand, hard physical training was not significantly protective. Results were similar for Alzheimer’s disease alone. Results for the co-twin control analysis were not statistically significant, possibly in this instance due to low power.

Although what first comes to mind may be cardiovascular benefits, Erickson et al. (2011) have demonstrated in non-demented older adults that after one year of aerobic exercise in the form of walking, the volume of the hippocampus is increased compared to a control group, and this correlates with higher brain-derived neurotropic factor (BDNF). In other words, a benefit of exercise appears to be increased BDNF, which is important to brain plasticity and cognitive performance.
Diet and Supplements

The extent to which protective effects can be identified associated with particular foods or dietary supplements is among the more elusive areas of study (Daviglus et al., 2010; Mayeux & Stern, 2012). In the 1967 Swedish Twin Registry questionnaire participants were asked what part of their diet consisted of fruits and vegetables—“great part,” “medium part,” “small part,” or “no part.” Categories were collapsed into medium and great vs. small or no. In the case control condition, a “medium” or “great” proportion of fruit and vegetables in the diet was associated with a decreased risk of Alzheimer’s disease OR 0.60 (0.41-0.86) and all dementia OR 0.73 (95%CI 0.53-1.00). However, stratified analyses indicated that protective effect of fruit and vegetable consumption was observed for women but not for men.

Conclusion

What are the implications of the results from the Swedish Twin studies and the conclusions of the various review panels? 1. Alzheimer’s disease risk is strongly influenced genetically. 2. Non-genetic influences that increase risk of dementia and Alzheimer’s disease include early and midlife exposures. Risk factors in early life include inflammation and other adverse circumstances, while those in midlife include diabetes, cholesterol, and overweight. 3. Protective and delaying factors occur from early life through old age. These include education, occupation, physical activity and cognitively engaging activities. 4. The most intuitive risk and protective factors may be the least important. The best evidence across different reviews for potentially modifiable risk and protective factors currently points to diabetes and other vascular risk factors and to physical exercise. 5. Much evidence comes from prospective observational studies. Results from randomized clinical trials have been disappointing, but will always be limited simply because Alzheimer’s disease develops slowly over a long period of time. 6. It may be possible to distinguish between protective factors that act on the causes of Alzheimer’s disease or other dementias and delaying factors that do not affect the disease process but do affect the clinical manifestation. 7. Whether and when any one person develops Alzheimer’s disease or other dementia represents a life time of genetic and environmental or behavioral influences. Figure 3 presents a
summary of risk and protective factors. Healthy lifestyles may help to maintain cognitive health but are no guarantee against Alzheimer’s disease. However, life style changes may delay the manifestation of dementia, thereby lowering the burden on the affected persons, caregivers and the rest of society.
Endnote

1. The results of these analyses are presented as odds ratios (OR) with 95% confidence intervals (CI). When the CI is greater than 1.0, the factor constitutes a significant risk; when the CI is less than 1.0, the factor is significantly protective. When the CI straddles 1.0, the factor is not significantly associated with risk of dementia. An OR of 3.00 may be interpreted as tripling one’s odds of disease.
References


Figure 1. Heuristic model of influence of non-genetic risk and protective factors is on the age-related trajectory of cognition. The black line shows gradual loss of cognitive reserve over age, with an individual crossing the threshold first into mild cognitive impairment and subsequently into dementia.

Figure 2. Scorecard for putative risk and protective factors for dementia.

NOTES: ☐ indicates sufficient evidence for a particular risk (RED) or protective (GREEN) factor; blank cells indicate factors where either explicitly or implicitly the source found the evidence insufficient. Factors explicitly excluded from consideration by a source are indicated by an X in that cell.

SOURCES: CDC = Centers for Disease Control and Prevention and the Alzheimer’s Association; NIH = National Institutes of Health State-of-the-Science Conference Statement; PSPI = Psychological Science in the Public Interest; CSH = Cold Spring Harbor Perspectives in Medicine.

Figure 3. Heuristic model of dementia risk and protective factors across the life span.
<table>
<thead>
<tr>
<th>Health Factor</th>
<th>CDC</th>
<th>NIH</th>
<th>PSPI</th>
<th>CSH</th>
<th>Swedish Twins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High blood pressure</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated cholesterol</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Body mass index (overweight and obese)</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic head injury</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Depression, chronic stress, neuroticism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inflammation</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Level of education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive engagement, mentally stimulating activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupational complexity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet (Mediterranean, low fat, high fruit and vegetable)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social engagement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>